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Investigation of the effect of lacosamide on renal function: A 5-Year retrospective cohort study

Lacosamide and renal function tests

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Abstract
Aim: Lacosamide, a third-generation antiepileptic drug, is used as adjunctive treatment of partial-onset seizures. It is mainly eliminated through the kidneys. The drug acts by enhancing the slow inactivation of voltage-gated sodium channels. The aim of this study was to investigate the long-term effects of lacosamide on renal function.
Material and Methods: The study included two groups of patients with epilepsy (those treated and those not treated with lacosamide) and a healthy control group. Plasma creatinine, blood urea nitrogen, glomerular filtration rate (GFR; by the Modification of Diet in Renal Disease formula), and sodium levels were calculated for the participants at four retrospective time points over 6 years (t0-t1-t2-t3).
Results: A total of 123 (female/male=58/65) participants, with a mean age of 33.9±9.5 years, were included in the study. The study covered a total period of 57.7±5.5 months. GFRs calculated at all time points for the group receiving lacosamide (GFR0:123.1 mL/min/1.73m2, GFR1:115.1 mL/min/1.73m2, GFR2:112.9 mL/min/1.73m2, and GFR3:102.3 mL/min/1.73m2) were lower than those of the healthy control group ($p<0.05$). GFR 3 levels was calculated to be lower in patients treated with lacosamide than in patients not treated with lacosamide (p<0.05).On performing statistical analysis, higher plasma Cr0.2.3 levels were found for the group using lacosamide compared to the healthy control group ($p<0.05$).
Discussion: In this study, all parameters evaluated to investigate the effect of lacosamide on renal functions were found to be within normal ranges in each group. However, plasma GFR levels were found to be lower in the group using lacosamide compared to the control group.

Keywords
Lacosamide, Antiepileptic Drugs, GFR, Sodium Channel Blocker, Seizure

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Introduction

Epilepsy treatment usually begins as monotherapy. However, in case of uncontrolled seizures, adjunctive drugs are added to the therapy. In 30%–40% of patients with epilepsy, seizures cannot be fully controlled despite the administration of antiepileptic drug (AED) polytherapy [1]. Lacosamide, a third-generation AED, can be administered to patients who still have uncontrolled seizures despite the use of at least two AEDs. Lacosamide was approved by the U.S. Food and Drug Administration (FDA) in 2008 as an adjunctive therapy for patients with partial-onset epilepsy aged ≥17 [2]. When administered adjunctively at a dose of 200–600 mg/day in the treatment of motor and non-motor focal seizures, with or without awareness, lacosamide can significantly reduce the frequency of seizures due to the fast onset of its anticonvulsant effect [3]. It has a well-known pharmacokinetic profile [4]. Oral lacosamide has a bioavailability of approximately 100% and reaches peak plasma concentration in 1–4 h [5]. Lacosamide is eliminated from the systemic circulation mainly by the excretory system and biotransformation. Dose adjustment is not required for lacosamide in adult and pediatric patients with a glomerular filtration rate (GFR) of >30 mL/min/1.73m2 [6]. Lacosamide has a more favorable side-effect profile than some older AEDs, with dizziness, headaches, and nausea as the most common side effects [7]. Antiepileptic drugs are usually used for an extended period of time or for life. Some side effects or metabolic changes may occur years later. This study investigated the effect of lacosamide on renal functions over a period of approximately 5 years. GFR, used in the diagnosis, follow-up, and evaluation of renal diseases, is considered the best indicator of renal function [8]. The Modification of Diet in Renal Disease (MDRD) formula was used to calculate GFR [9]. The study included three groups: one group using at least two AEDs + lacosamide, one group using at least two AEDs, and another group composed of healthy individuals. The groups were compared in terms of changes in serum GFR and creatinine (Cr) levels at time points t0, t1, t2, and t3. Our study aimed to show the long-term effects of lacosamide on renal function. Our hypothesis was that GFR would tend to decrease further over time in the group using lacosamide.

Material and Methods

This research was designed as a retrospective cohort study. The study enrolled patients who were regularly monitored at the epilepsy outpatient clinic of a tertiary health-care center. The study was approved by the ethics committee (on 14.12.2021, decision number: 2021/2847) and performed in accordance with the criteria of the Helsinki Declaration. Informed consent forms were obtained from the participants.

In this study, patients were divided into three groups. The first group included patients with epilepsy who received at least two AEDs along with lacosamide. The second group comprised patients with epilepsy who received at least two AEDs other than lacosamide. Finally, the study also included a control group consisting of healthy individuals who did not use any AED. Clinical information and laboratory parameters were screened using electronic files of patients followed up for epilepsy between 01.01.2013 and 01.12.2021. Those who were included in the healthy control group were randomly selected amongst individuals who had at least four records over a 6-year period in the electronic database. Epilepsy diagnosis was confirmed based on the International League Against Epilepsy 2014 guideline [10]. Inclusion criteria were as follows: a confirmed diagnosis of epilepsy, age over 18 years, using at least two AEDs, and having lacosamide therapy initiated at our center. The exclusion criteria were as follows: failure to use AEDs regularly, consistently taking medications due to a chronic disease other than epilepsy, less than one follow-up per year as per outpatient clinic records, a history of acute or chronic renal failure, and having undergone epilepsy surgery. Patients who were found to use lacosamide for a short period of time (<4 years), those who were switched to a lower AED dose, or those who stopped using AED were rejected from the study. The number of patients was determined as follows: G-Power analysis was used; GFR of 102±17 mL/min/1.73m2 for the patient group and GFR of 119±24 mL/min/1.73m2 for the control group. Accordingly, with an effect size of 0.817, α of 0.05, and 1-β error probability of 0.95, it was found that a minimum of 40 patients must be included in the study.

Venous blood samples were collected in ethylenediaminetetraacetic acid-containing tubes after a 12-h fasting duration to evaluate the laboratory parameters of the patients and control group. The blood samples were analyzed using Beckman Coulter® AU 5800. Participants' serum Cr levels were recorded. GFR was calculated according to the following MDRD formula: 175 × [(Serum Cr) − 1.154] × [(Age) − 0.203] × (0.742 if female) × (1,212 if African American) [9]. In this formula, the GFR unit is mL/min/1.73 m2, and all GFR results in the study are presented accordingly. The parameters obtained were evaluated at four time points. Time point t0 indicates the week when lacosamide was initiated for the first group, and at least 49 months back for the other groups. t1, t2, and t3 indicate the period between 18–30 months, 31–48 months, and 49–72 months, respectively. Laboratory data pertaining to the three groups were categorized in accordance with these time points. The parameters mentioned in the article are tagged using the same system (e.g., GFR1, Cr3)

Statistical Analysis

The data obtained at the end of the data collection phase were transferred to a computer for analyses. SPSS® 26.0 (SPSS Inc., Chicago, IL, USA) software suite was used for statistical analysis. Numerical data are presented as arithmetic mean, standard deviation, and minimum and maximum values, and categorical data are presented as frequency distributions and percentages. Means were compared among the groups, and analysis of variance and Eta coefficient test were used for evaluating daily doses of AED, age, and t, t2, and t3 periods. Multivariate Post Hoc analysis was performed to compare laboratory results among the groups. The Chi-square test was used to compare categorical data (gender and frequency of use of AED types across groups). Statistical significance was set at $p < 0.05$.

Results

The study included 44 (35.8%) patients with epilepsy using at least two AEDs + lacosamide, 43 (35.0%) patients who

Table 1. Characteristics of participants and time periods

	LCM+	LCM -	Control	Total
Age	34.4±10.2	32.8±10.1	34.8±7.7	33.9±9.5
Female	19 (15.4%)	20 (16.3%)	19 (15.4%)	58 (47.2%)
Male	25 (20.3%)	23 (18.7%)	17 (13.8%)	65 (52.8%)
Timeline*				
T1	23.4± 2.7	23.3±3.1	22.4± 3.1	23.1± 3.0
T2	38.6± 5.8	39.0±4.4	37.3± 4.4	38.2± 4.8
T3	58.1± 5.8	56.8± 5.2	58.3± 5.8	57.7± 5.5

Table 2. Current medications and daily doses of epilepsy patients

	LCM +	LCM -	Total	P
Valproic acid				
Yes	14 (16.3%)	18 (20.9%)	32 (37.2%)	0.504
No	29 (33.7%)	25 (29.1%)	54 (62.8%)	
· mg/day	1178± 385	1180± 427	1179± 402	0.989
Levetiracetam				
Yes	30 (34.5%)	24 (27.6%)	54 (62.1%)	0.274
No	14 (16.1%)	19 (21.8%)	33 (37.9%)	
· mg/day	2316± 875	1830± 843	2095± 887	0.042
Carbamazepine				
Yes	16 (18.6%)	15 (17.4%)	31 (36.0%)	1.000
No	27 (31.4%)	28 (32.6%)	55 (64.0%)	
· mg/day	752±341	720±280	737±309	0.769
Clobazam				
Yes	17 (20.2%)	8 (9.5%)	25 (29.8%)	0.094
No	27 (32.1%)	32 (38.1%)	59 (70.2%)	
· mg/day	25.5±10.5	25.0±5.3	25.4±9.1	0.884
Lamotirgine				
Yes	8 (9.2%)	10 (11.5%)	18 (20.7%)	0.605
No	36 (41.4%)	33 (37.9%)	69 (79.3%)	
· mg/day	337±176	182±141	251±172	0.055
Zonisamide				
Yes	4 (4.6%)	1 (1.1%)	5 (5.7%)	0.360
No	40 (46.0%)	42 (48.3%)	82 (94.3%)	
· mg/day	225±50	100±0	200±70	0.111
Topiramate				
Yes	2 (2.3%)	7 (8.0%)	9 (10.3%)	0.089
No	42 (48.3%)	36 (41.4)	78 (89.7%)	
· mg/day	200±0	157±60	166±55	0.374

LCM + :Lacosamide and at least two antiepileptic treatments, LCM - : At least two antiepileptic treatments without lacosamide

used AEDs other than lacosamide, and 36 (29.2%) healthy individuals. There were 58 (47.2%) females and 65 males (52.8%). Participants had a mean age of 33.9 years. For all the three groups, the first parameter evaluated for the first study was recorded as t 0 time. Average time periods for the groups were as follows: t 1 = 23.1 months, t 2 = 38.2 months, and t 3 = 57.7 months. There was no significant difference between the groups in terms of t 1 , t 2 , and t 3 . A strong correlation was observed between the groups in terms of age; gender distribution; and t 0 , t 1 , t 2 , and t 3 time points in which the parameters were studied (Table1). For patients with epilepsy using lacosamide and those not using it, doses of other AEDs and frequency of use were investigated. The current mean dose of lacosamide was analyzed as 298±100 mg/day. There was no significant difference between the two groups in terms of frequency of use and daily doses of valproic acid, levetiracetam, carbamazepine, clobazam, lamotrigine, zonisamide, and topiramate (p>0.05) (Table 2). Among these three groups, the results of renal functions (Cr, GFR) were evaluated using multivariate Post Hoc analysis (Table 3). In those using lacosamide, plasma Cr levels were t 0 : 0.70 mg/dL, t 1 : 0.69 mg/dL, t 2 : 0.76 mg/dL, and t 3 : 0.88 mg/dL. In individuals with epilepsy who did not use lacosamide, plasma Cr 0.1.2.3 levels were t 0 : 0.65 mg/dL, t 1 : 0,65 mg/dL, t 2 : 0.68 mg/dL, and t 3 : 0.75 mg/dL. On performing statistical analysis, higher plasma Cr 0.2.3 levels were found for the group using lacosamide compared to the healthy control group (p < 0.05). Additionally, plasma Cr 3 levels were found to be higher for the group using lacosamide as compared to the group using other AEDs (p<0.05). GFR results calculated according to the MDRD formula for the three groups, the principal result investigated in the study, were also

compared. Between groups that used lacosamide GFR 3 : 102.3 mL/min/1.73m 2 and not used GFR 3 : 115.9 mL/min/1.73m 2 (p<0.05). When GFR measurements were compared between the group using lacosamide and the control group, GFR was shown to be high in the control group for all four measurements (GFR 0.1.2.3) (p<0.05). There was no significant difference between the group that did not use lacosamide and the control group in terms of GFR 0.1.2.3 results (p>0.05).

Discussion

Lacosamide is a third-generation AED used as adjunctive therapy for partial-onset seizures in most countries. It was licensed in Turkey in 2012. In Turkey, its prescription is contingent on at least 6 months of combined use of two AEDs; hence, it is usually preferred as the third or fourth AED in drug-resistant epilepsy cases. [11]. Lacosamide is an amino acid (chemical formula: acetamido-N-benzyl-3-methoxypropionamide), and unlike other sodium channel blockers, it acts by selectively enhancing the slow inactivation of voltage-gated sodium channels. Thus, it results in a decrease in the pathological hyperexcitability of neurons without altering their physiological activity [12]. As a functionalized amino acid compound with linear pharmacokinetics, lacosamide has 100% oral absorption in adults and demonstrates a low plasma protein binding of <15%. It has a half-life of 13 h and reaches peak blood concentration within 1–2 h. It is mainly excreted via the kidneys and has no known drug-drug interaction [13]. Clinical studies have shown that lacosamide does not affect plasma levels of carbamazepine, valproic acid, lamotrigine, levetiracetam, oxcarbazepine, and phenytoin to a certain extent [14]. This property of lacosamide has contributed to the reliability of our work. In other words, renal function and electrolytes of the group using lacosamide were minimally affected by other AEDs. In this study, the inclusion of a control group composed of healthy individuals enabled performing comparisons between the group using lacosamide and other AEDs and the control group.

Our study found strong correlations between the distribution of gender and mean age among the three groups. This result

Table 3. Evaluation of renal function tests according to timeline between groups

	Groups		Mean	Mean Difference (I-J)	Std. Error	p	95% Confidence Interval	
							Lower B.	Upper B.
GFR0	LCM +	LCM -	128,2 ± 22,3	-5,04	5,061	0,322	-15,06	4,99
		Control	134,7 ± 27,0	-11.59*	5,24	0,029	-21,97	-1,21
	Control	LCM -	128,2 ± 22,3	6,55	5,325	0,221	-3,99	17,1
		LCM +	123,1 ± 20,1	11.59*	5,24	0,029	1,21	21,97
GFR1	LCM +	LCM -	121,1 ± 21,3	-6,03	4,258	0,159	-14,46	2,4
		Control	124,4 ± 23,2	-9.38*	4,409	0,035	-18,11	-0,65
	Control	LCM -	121,1 ± 21,3	3,35	4,481	0,456	-5,52	12,22
		LCM +	115,1 ± 13,8	9.38*	4,409	0,035	0,65	18,11
GFR2	LCM +	LCM -	121,1 ± 18,7	-8,87	4,763	0,065	-18,3	0,56
		Control	125,0 ± 27,9	-12.76*	4,931	0,011	-22,52	-2,99
	Control	LCM -	121,1 ± 18,7	3,89	5,012	0,44	-6,04	13,81
		LCM +	112,9 ± 27,9	12.76*	4,931	0,011	2,99	22,52
GFR3	LCM +	LCM -	115,9 ± 20,6	-13.56*	4,664	0,004	-22,8	-4,33
		Control	120,6 ± 28,4	-18.31*	4,829	0,001	-27,87	-8,75
	Control	LCM -	115,9 ± 20,6	4,74	4,907	0,336	-4,97	14,46
		LCM +	102,3 ± 14,6	18.31*	4,829	0,001	8,75	27,87
Cr0	LCM +	LCM -	0,65 ± 0,10	0,044	0,0325	0,175	-0,02	0,109
		Control	0,60 ± 0,15	.095*	0,0308	0,003	0,034	0,156
	Control	LCM -	0,65 ± 0,10	-0,05	0,0318	0,118	-0,114	0,013
		LCM +	0.70 ± 0,11	-.095*	0,0308	0,003	-0,156	-0,034
Cr1	LCM +	LCM -	0,65 ± 0,09	0,036	0,0292	0,218	-0,022	0,094
		Control	0,66 ± 0,10	0,031	0,0277	0,266	-0,024	0,086
	Control	LCM -	0,65 ± 0,09	0,005	0,0286	0,854	-0,052	0,062
		LCM +	0,69 ± 0,13	-0,031	0,0277	0,266	-0,086	0,024
Cr2	LCM +	LCM -	0,68 ± 0,11	0,074	0,0403	0,068	-0,006	0,154
		Control	0,61 ± 0,15	.147*	0,0381	0,001	0,071	0,222
	Control	LCM -	0,65 ± 0,09	-0,072	0,0395	0,07	-0,151	0,006
		LCM +	0,76 ± 0,18	-.147*	0,0381	0,001	-0,222	-0,071
Cr3	LCM +	LCM -	0,75 ± 0,14	.130*	0,0494	0,01	0,032	0,228
		Control	0,65 ± 0,20	.232*	0,0467	0,001	0,139	0,325
	Control	LCM -	0,75 ± 0,14	-.102*	0,0484	0,038	-0,198	-0,006
		LCM+	0,88 ± 0,21	-.232*	0,0467	0,001	-0,325	-0,139

Post Hoc Multiple Comparisons for observed means. * The mean difference is significant at the .05 level. GFR: Glomerular Filtration Rate (mL/min/1.73 m2), Cr: Serum Creatinine (mg/dL), LCM + : Lacosamide and at least two antiepileptic treatments, LCM - : At least two antiepileptic treatments without lacosamide

suggests that age and gender-related variables would have a minimal effect on the parameters analyzed in this study. In addition, there was no significant difference between the time points (t0, t1, t2, and t3) used in this study.

Studies showed that factors such as renal function, gestational status, age, and critical diseases may affect the pharmacokinetics of lacosamide. Indeed, our main goal in this study was to analyze the effect of lacosamide on renal functions. The normal range of GFR is 120±25 mL/min/1.73m2 for men and 95 ± 20 mL/min/1.73m2 for women [17]. It has been reported that there is currently no need to monitor renal functions when lacosamide is used [4]. Other studies have suggested that dose adjustment is not required for lacosamide in adult and pediatric patients with GFR of > 30mL/min/1.73m2 [6].

In our study, we evaluated long-term effects of lacosamide on GFR among the study groups. We compared the GFR results of the group using lacosamide and the healthy control group. Although the GFR values of the groups were within normal limits, we have achieved a very assertive result. GFR results measured at all time points (GFR0.1.2.3) were found to be lower in those who used lacosamide compared to the healthy control group ($p < 0.05$). There was no clear difference between patients with epilepsy receiving AEDs other than lacosamide and the healthy control group. Between these two groups, only GFR3 results were low in the group of patients with epilepsy who did not use lacosamide. The healthy control group had GFR3: 120.6 mL/min/1.73m2, whereas the group receiving AEDs other than lacosamide had GFR3: 115.9 mL/min/1.73m2 ($p < 0.05$). Based on this result, we tend to think that other AEDs also result in lower GFRs after a certain period of time. However, this hypothesis should be backed up with clearer evidence. We compared patients with epilepsy among themselves based on the GFR result. The group that received lacosamide as part of its therapy had lower GFR3 (102 mL/min/1.73m2) compared to the group that did not receive it (115.9 mL/min/1.73m2) ($p < 0.05$). The data in the study covers a period of average 57.7 ± 5.5 months. During the follow-up period of approximately 5 years, the GFR level remained within the normal range in all three groups. However, GFR results were found to be lower in the group using lacosamide compared to the other two groups. A 2013 study involving healthy volunteers and patient groups

investigated the effects of lacosamide on renal functions and its correlation with plasma drug concentrations. Accordingly, it was found that in those with decreased renal function, drug clearance was also reduced, and as a result, the plasma concentration of lacosamide increased. The same study advised reducing the drug dose in those with renal dysfunction [18]. Current publications discuss plasma concentrations of the drug or the use of follow-ups with renal function tests in those who use lacosamide. A paper published in 2020 stated that renally excreted drugs such as lacosamide can accumulate in the body and cause toxicity with a decrease in renal function [4]. That study emphasized that therapeutic drug monitoring (TDM) could help prevent a drug from reaching toxic concentrations [4]. However, no advice has been given as to when TDM should start or how frequently it should be performed for lacosamide. Another study published in 2021 emphasized that TDM should be performed for lacosamide in those with severe renal dysfunction, and its dose should be calculated based on renal function [19]. This can prevent the drug from causing side effects associated with high plasma concentrations. Based on these current studies, we can recommend monitoring the plasma concentration of lacosamide in those with moderate-to-severe renal dysfunction. In our study, no renal dysfunction was detected in any of the participants. Accordingly, we can contend that the risk of developing any renal dysfunction is very low in patients with epilepsy receiving lacosamide + at least two AEDs over a period of approximately 5 years.

This study has some limitations. First, not every patient was treated with an equal dose of lacosamide. Second, the AEDs used by the two groups other than lacosamide were not the same. Finally, it is not known whether participants used any drug for a short period of time (e.g., painkillers, flu medications, and antibiotics) during the period when their blood was analyzed in the laboratory.

Conclusion

In this study, we investigated the effects of lacosamide, one of the latest AEDs used in Turkey, on renal functions. For about 5 years, it was observed that lacosamide did not reduce GFR below the normal range. However, GFRs were found to be lower in those who received lacosamide at all time points compared to the control group. There are few studies in the literature investigating the long-term effects of lacosamide on renal functions. Therefore, more comprehensive and long-term cohort studies are needed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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